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A meta-analysis on
myo-inositol effect in PCOS

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Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials

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Abstract

Myo-inositol (MI) supplementation in women with polycystic ovary syndrome (PCOS) has been evaluated over the last years. Many hormonal and reproductive impairments associated with this disorder seem relieved by the supplement. The objective of the meta-analysis was to assess the effects of MI alone or combined with D-chiro-inositol (DCI) on the endocrine and metabolic abnormalities of women with PCOS. Literature was retrieved from selected databases, MEDLINE, EMBASE, PubMed and Research Gate (up to November 2016). Only randomized controlled trials (RCTs) investigating the effects of MI alone or combined with DCI were reviewed. Nine RCTs involving 247 cases and 249 controls were included. Significant decreases in fasting insulin (SMD = $-1.021 \mu\text{U/mL}$, 95% CI: -1.791 to -0.251 , $P=0.009$) and homeostasis model assessment (HOMA) index (SMD = -0.585 , 95% CI: -1.145 to -0.025 , $P=0.041$) were identified after MI supplementation. The trial sequential analysis of insulin meta-analysis illustrates that the cumulative z-curve crossed the monitoring boundary, providing firm evidence of the intervention effect. A slight trend toward a reduction of testosterone concentration by MI with respect to controls was found (SMD = -0.49 , 95% CI: -1.072 to 0.092 , $P=0.099$), whereas androstenedione levels remained unaffected. Throughout a subgroup's meta-analysis, a significant increase in serum SHBG was observed only in those studies where MI was administered for at least 24 weeks (SMD = 0.425 nmol/L , 95% CI: 0.050 – 0.801 , $P=0.026$). These results highlight the beneficial effect of MI in improving the metabolic profile of women with PCOS, concomitantly reducing their hyperandrogenism.

Key Words

- myo-inositol
- D-chiro-inositol
- inositol
- polycystic ovary syndrome
- insulin

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Introduction

Myo-inositol (MI) is one stereoisomer of a C₆ sugar alcohol that belongs to the inositol family (1). It is the precursor of inositol triphosphate, acting as an intracellular second messenger and regulating a number of hormones such as thyroid-stimulating hormone, follicle-stimulating hormone (FSH) and insulin (2).

MI and D-chiro-inositol (DCI), another stereoisomeric form of inositol, balance in different ways some metabolic

deregulations concurring with insulin resistance (IR) (3): MI-derived phosphoinositol-3-phosphate (PIP3) enhances glucose transport inside the cells through the stimulation of GLUT4 translocation to the cell membrane. Its derivative inositolphosphoglycan (MI-IPG) plays a pivotal role in downregulating the release of free fatty acids (FFA) from adipose tissues, hindering the enzyme adenylate cyclase. Indeed, FFA are known to reduce glucose

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disposal, causing IR and increased triglyceride synthesis. DCI upregulates pyruvate dehydrogenase leading to the production of ATP by the Krebs' cycle. MI and DCI promote glycogen synthase, inducing glucose conversion to glycogen stored inside cells. MI modulates the activation of glucose transporters and glucose utilization, and glycogen synthesis takes place under the control of DCI. This molecule on the ovary regulates the insulin-induced androgen synthesis, whereas MI regulates glucose uptake and FSH signaling (1).

In view of its recognized insulin-sensitizing activity, MI has been used to prevent and/or treat a number of metabolic disorders related to IR, such as the metabolic syndrome (4, 5), gestational diabetes mellitus (6, 7, 8, 9, 10) and the polycystic ovary syndrome (PCOS) (11, 12, 13).

PCOS is a heterogeneous endocrine, reproductive and metabolic disorder, affecting at least 5–10% of the total population of reproductive-age women, worldwide (14). Independently of body habitus (15), women with PCOS manifest a 50–70% incidence of IR, resulting in a compensatory hyperinsulinemia, which derives many of the phenotypic features of this disease. PCOS encompasses a broad spectrum of biochemical/clinical signs and symptoms such as irregular menstrual cycles, polycystic ovaries, acne, overweight, androgen excess with consequent hirsutism and as aforementioned IR (16, 17). It is also associated with several long-term health consequences, including obesity (18, 19), infertility (20), obstetric complications (21), type 2 diabetes (22, 23, 24), cardiovascular disease (24, 25, 26, 27), psychological distress (28) and ostensibly mood disorders (29, 30). A meta-analysis also reported the association between women with PCOS and cancer of the endometrium and ovarian cancer (31).

It is noteworthy that improvement of IR and reduction of circulating insulin are key therapeutic targets in PCOS (32), enhancing fertility and reducing the lifelong risk for type 2 diabetes and early cardiovascular disease. Besides metformin, MI is now considered as a further insulin-sensitizing supplement which could benefit women with PCOS (33, 34). Exercises and a healthy nutritional lifestyle have widely been gathering attention in the management of PCOS. Although robust data should be addressed in further investigation, a study showed beneficial effects in patients affected by obesity and type 2 diabetes following either a Mediterranean or ketogenic diet (35).

While there are numerous uncontrolled reports, the effects of supplementation with MI in PCOS have also been evaluated in randomized controlled trials (RCTs). A protocol

critically reviewing the existing literature has been published within the Cochrane Reviews (36). The present meta-analysis would identify RCTs of supplementation with MI alone or combined with DCI in PCOS, with the aim to assess the effectiveness of such treatments in restoring the metabolic and endocrine profiles.

Materials and methods

Search strategy and data sources

We performed a literature search of MEDLINE, EMBASE, PubMed and Research Gate for studies published in any language up to November 2016. We used the following combination of medical subject headings, terms and free text words: 'inositol', 'MI', 'DCI', 'PCOS' and 'IR'. Only RCTs evaluating the supplementation of MI alone or in association with DCI in women with PCOS were eligible. In addition, reference lists of published reviews were reviewed in order to identify additional eligible studies. We followed the PRISMA checklist for meta-analysis (38).

Inclusion and exclusion criteria

Articles were critically reviewed for their eligibility in the meta-analysis by the two of us (B O and F F). Among all the collected articles, RCTs were identified by reading titles, abstracts and study design to select relevant studies for inclusion/exclusion criteria. Inclusion criteria restricted the search to: (a) the population of interest was women with PCOS, (b) the intervention was MI with or without DCI, (c) assessment of fasting insulin concentrations, HOMA index, testosterone, androstenedione and/or sex hormone-binding globulin (SHBG) plasma levels. Exclusion criteria were: (a) articles describing MI treatments in combination with other drugs/supplements, (b) duplicate publications, and duplicates on different database, (c) review papers and (d) animal or cell culture studies.

Outcomes of interest

Primary outcomes: fasting insulin concentrations. Secondary outcomes: HOMA index, testosterone, androstenedione and SHBG plasma levels.

Data extraction and quality evaluation

The following data were extracted from the full text of selected studies and cross-checked by two researchers

(B O and F F): general characteristics of the study (first author's name, country where the study was conducted, study design, number of cases and controls, body mass index, inclusion/exclusion criteria, lifestyle changes, type and duration of treatment) and results (means and s.d./s.e. for each outcome after intervention from treatment vs control). The quality of reports was evaluated according to the methods recommended by the Cochrane Handbook 5.0.2. (37), including assessments of the randomization process, allocation concealment, blinding, selection criteria, baseline characters and withdrawal/dropouts.

Statistical analysis

The effect size was measured as the standardized mean difference (SMD) obtained as Hedges' *g*. An SMD less than 0 was considered as a positive size effect for outcomes, such as fasting serum insulin, HOMA and serum testosterone and androstenedione concentrations; an SMD greater than 0 was considered as a positive size effect for the serum SHBG outcome. The heterogeneity analysis of intervention was performed by the Cochran's *Q* test and the *I*² statistic, using a *P* value=0.10. In order to account for heterogeneity across studies, the Der Simonian and Laird random effect model was used to obtain the pooled estimates and their 95% confidence intervals (CIs). To examine a potential source of variation, subgroup meta-analyses were performed according to treatment duration, i.e. 12–16 weeks or 24 weeks. Forest plots were used to visually show the results of the analyses performed. Meta-analysis was evaluated by the use of Stata Statistical Software: Release 12 (College Station, TX, USA: StataCorp LP). Results were considered statistically significant when the two-sided *P* value was <0.05.

Trial sequential analysis (TSA)

The TSA was performed for the insulin outcome in order to confirm the result obtained in the traditional meta-analysis. The cumulative *z*-curve was calculated with a random effect model and the type I error (α) was set as 5% with a power of 80%. The sequential monitoring boundaries were based on the O'Brien Fleming type alpha spending function and the heterogeneity correction was model-variance-based. The analysis was conducted with the use of TSA software 0.9.5.5 Beta (Copenhagen Trial Unit, Copenhagen, Denmark).

Results

Literature search and characteristics of included studies

The flow diagram of the meta-analysis is presented in Fig. 1 (38). In the initial search, 104 potentially relevant articles were identified, and 94 studies remained after removing duplicates. Through a preliminary screening, 76 records were excluded because they did not meet the inclusion/exclusion criteria. The remaining 18 articles were assessed for eligibility, and 9 articles which met the criteria were finally included in the meta-analysis. Studies were excluded for several reasons including (a) data of the outcome were unavailable or not expressed in the numerical form (39), (b) patients were treated with MI combined with other molecules such as multivitamin complex (40), lactoferrin and bromelin (41) or oral contraceptives pills (OCPs) (42), (c) menopausal women with metabolic syndrome (4, 5) and (d) the study was a non-randomized design (43, 44, 45).

Characteristics of the included studies are summarized in Table 1. Studies were conducted in Italy (46, 47, 48, 49, 50, 51, 52), Georgia (53) and Turkey (54) and were published between 2007 and 2016. Treatments

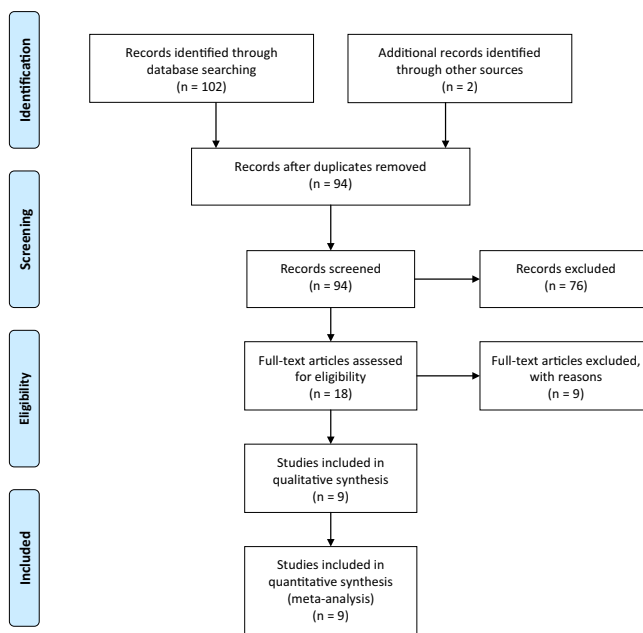


Figure 1

PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of study selection (38). Reproduced under the terms of the Creative Commons Attribution License from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009 6 e1000097. (doi:10.1371/journal.pmed1000097)

Table 1 Characteristics of the included studies.

Study's first author	Country	Study design	N° of subjects	BMI baseline	Inclusion criteria	Exclusion criteria	Lifestyle changes	Treatment	Duration (weeks)
Genazzani et al. (48)	Italy	RCT	(N=20) Treated: 10 Control: 10	29 ± 1.6 27.8 ± 2.1	PCOS, oligo/amenorrhea, PRL range 5–25 ng/mL, mild to severe hirsutism and/or acne	Hormone treatments in the last 24 weeks; adrenal enzymatic deficiency and/or other endocrine disease	N	MI + FA vs FA	12
Costantino et al. (47)	Italy	DBRCT	(N=42) Treated: 23 Control: 19	22.8 ± 0.3 22.5 ± 0.3	Age: <40 years, PCOS, oligomenorrhea, high serum-free T and/or hirsutism	Not described	N	MI + FA vs FA	12–16
Gerli et al. (49)	Italy	DBRCT	(N=92) Treated: 45 Control: 47	35 35.2	Age: <35 years, PCOS according to Adams and coworkers criteria (56), oligo/amenorrhea	Hyperprolactinemia, abnormal thyroid function tests, congenital adrenal hyperplasia	N	MI + FA vs FA	16
Artini et al. (46)	Italy	RCT	(N=50) Treated: 25 Control: 25	28 ± 1.6 26.6 ± 2.1	PCOS, oligo/amenorrhea, PRL range 5–25 ng/mL, mild to severe hirsutism and/or acne	Hormone treatments in the last six months; adrenal enzymatic deficiency and/or other endocrine disease	N	MI + FA vs FA	12
Pizzo et al. (50)	Italy	DBRCT	(N=50) Treated: 25 Control: 25	25.1 ± 5.2 24.37 ± 5.31	PCOS according to Rotterdam's criteria	Adrenal cortex hyperplasia, Cushing syndrome, non-classical deficiency of 21-hydroxylase, Addison syndrome, hypoadrenocorticism, hypothyroidism, hyperprolactinemia	N	MI + FA vs DCI + FA	24
Pkhaladze (53)	Georgia	RCT	(N=40) Treated: 20 Control: 20	22.3 ± 3.08 22.74 ± 3.75	Age: 13–19 years, PCOS according to Rotterdam's criteria	Patients within two years of menarche	Y	MI + FA vs OCPs	12
Ozay et al. (54)	Turkey	RCT	(N=106) Treated: 52 Control: 54	25.33 ± 5.20 23.79 ± 4.24	PCOS according to the Rotterdam criteria	Smoking, hyperprolactinemia, hypogonadotropic hypogonadism, pregnancy, thyroid disease, congenital adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome	N	MI + FA vs COC	12
Nordio and Proietti (51)	Italy	RCT	(N=50) Treated: 26 Control: 24	27.5 ± 2.9 27.7 ± 2.3	Age: <41 years, BMI >27 kg/m ² , PCOS according to Rotterdam criteria	Diabetic subjects, smokers and alcohol users	N	MI + DCI vs MI	24
Benelli et al. (52)	Italy	RCT	(N=46) Treated: 21 Control: 25	32 ± 4.8 31 ± 4.6	Age: <35 years, BMI >30 kg/m ² , PCOS according to Rotterdam criteria	Diabetic subjects, smokers and alcohol users	N	MI + DCI vs FA	24

BMI, body mass index; COC, combined oral contraceptive; DBRCT, double-blind randomized controlled trials; DCI, D-chiro-inositol; FA, folic acid; MI, myo-inositol; N, No; OCPs, oral contraceptive pills; RCT, randomized controlled trials; Y, Yes.



Table 2 Quality assessment of included trials.

Study	Randomization	Allocation concealment	Blinding	Selection criteria described	Comparable baseline	Withdrawal dropout described
Genazzani et al. (48)	M	Unclear	N	Y	Y	Unclear
Costantino et al. (47)	M	Unclear	Y, double-blind	Y	Y	Unclear
Gerli et al. (49)	Y, computer-generated	Unclear	Y, double-blind	Y	Y	Y
Artini et al. (46)	Y, computer-generated	Y, sealed numbered envelopes	Unclear	Y	Y	Y
Pizzo et al. (50)	M	Unclear	Y, double-blind	Y	Y	Unclear
Pkhaladze et al. (53)	M	N	N	Y	Y	Unclear
Ozay et al. (54)	Y	Unclear	N	Y	Y	M
Nordio and Proietti (51)	M	N	N	Y	Y	Unclear
Benelli et al. (52)	M	Unclear	N	Y	Y	Unclear

Evaluation according to the methods recommended by the Cochrane Handbook 5.0.2 (37).

M, the method was mentioned, but there was not detailed description; N, the method was not used in the study; Unclear, no relevant information was found in the study; Y, the method was reported with detailed description.

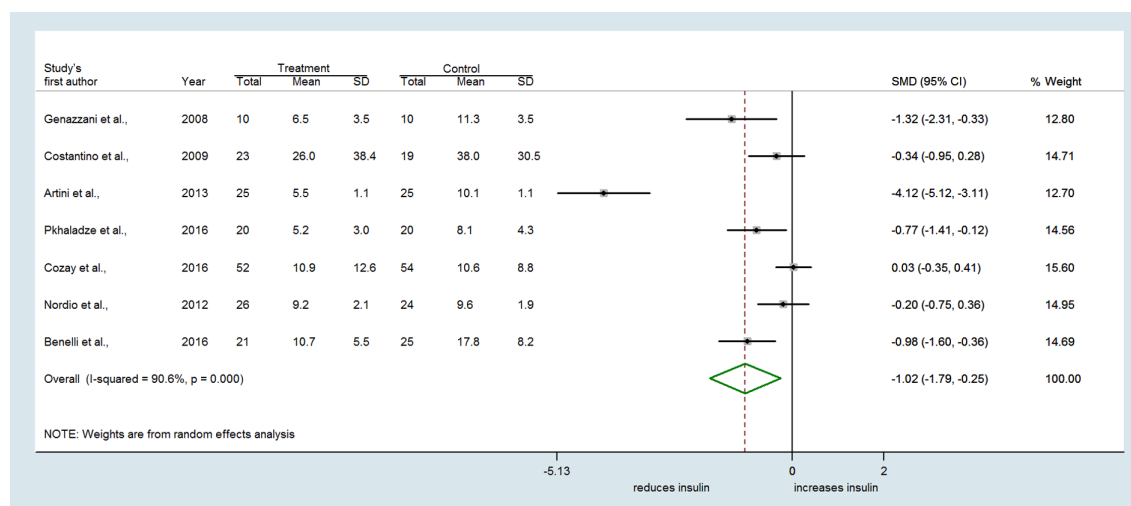
administered were MI + folic acid (FA) vs FA (46, 47, 48, 49), MI + FA vs DCI + FA (50), MI + DCI vs MI (51), MI + DCI + FA vs FA (52), and MI + FA vs OCPs (53, 54). The daily dose of MI supplementation ranged from 1.1 g to 4 g, and the durations of treatment ranged from 12 to 24 weeks. Either Rotterdam (55) or Adams and coworkers diagnostic criteria (56) were applied for the diagnosis of PCOS. The overall methodological study quality is summarized in Table 2.

The meta-analysis

In the nine selected studies, a total of 247 women with PCOS received MI alone or combined with FA or DCI, and 249 women received FA or other treatments (i.e. DCI, OCPs). The overall SMD estimated from seven studies showed

a significant decrease in fasting insulin in PCOS women who received MI compared to those who received FA or other treatments (SMD = -1.021 μ U/mL, 95% CI: -1.791 to -0.251, $P=0.009$) (Fig. 2). Considerable heterogeneity among studies was found ($Q=63.85$, $df=6$, $I^2=90.6\%$, $P<0.001$). Evidence of an MI effect was also identified for the HOMA index which decreased with treatment in the MI group compared to controls (SMD = -0.585, 95% CI: -1.145 to -0.025, $P=0.041$) (Fig. 3). Again, high heterogeneity across studies was found ($Q=37.84$, $df=6$, $P=84.1\%$, $P<0.001$).

Similarly, seven trials reporting the effect of MI on serum testosterone revealed substantial heterogeneity among studies ($Q=37.65$, $df=6$, $I^2=84.1\%$, $P<0.001$) (Fig. 4). A slight trend toward a reduction of testosterone

**Figure 2**

Forest plot showing effect sizes (standardized mean difference (SMD), 95% confidence interval (CI)) for fasting insulin in women with PCOS.

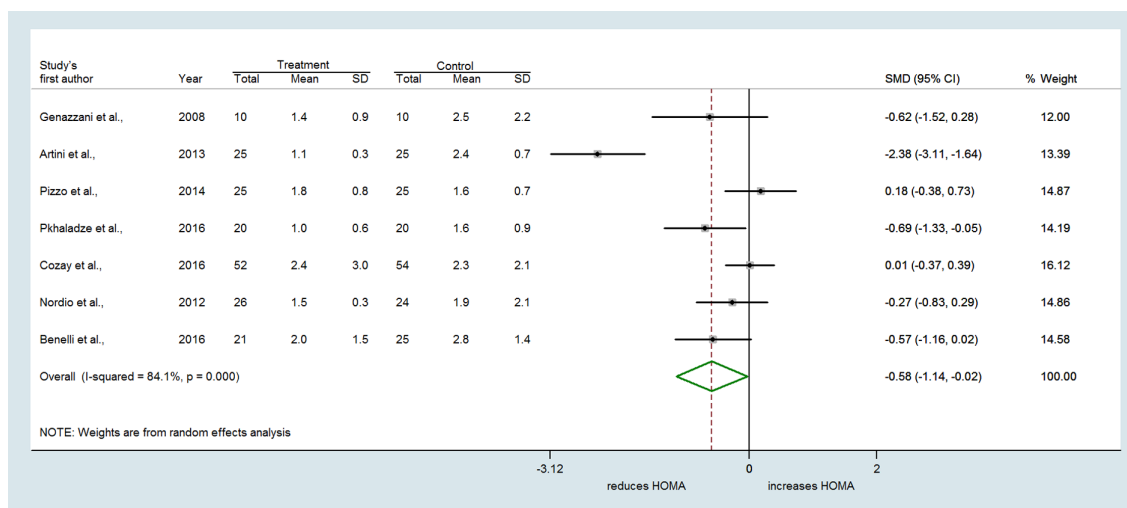


Figure 3
Forest plots showing effect sizes (SMD) for HOMA in women with PCOS.

concentrations by MI with respect to controls was found (SMD = -0.482, 95% CI: -1.052 to 0.088, $P=0.097$) (Fig. 4). Conversely, no difference between treatments was observed either for androstenedione (SMD = -0.097 ng/mL, 95% CI: -0.499 to 0.305, $P=0.635$) (Fig. 5) or SHBG levels (SMD = 0.166 nmol/L, 95% CI: -0.247 to 0.580, $P=0.430$) (Fig. 6).

A subgroup analysis was undertaken stratifying the studies by treatment duration. Treatment of MI up to 16 weeks had no significant effect on SHBG levels compared to controls (SMD = -0.016 nmol/L, 95% CI: -0.621 to 0.589, $P=0.958$) (Fig. 6). However, MI supplementation up to 24 weeks revealed a significant

increase in SHBG levels compared to other treatments (SMD = 0.418 nmol/L, 95% CI: 0.049–0.786, $P=0.026$) (Fig. 6). After stratification, heterogeneity was substantial among RCTs lasting 12–16 weeks ($Q=17.98$, $df=3$, $I^2=83.3\%$, $P<0.001$), whereas it was much lesser among those of longer duration ($Q=2.49$, $df=2$, $I^2=19.6\%$, $P=0.288$).

Results of TSA

The z-curve after the fourth trial crossed the sequential monitoring boundary providing firm evidence of an effect of MI on fasting insulin compared to controls (Fig. 7).

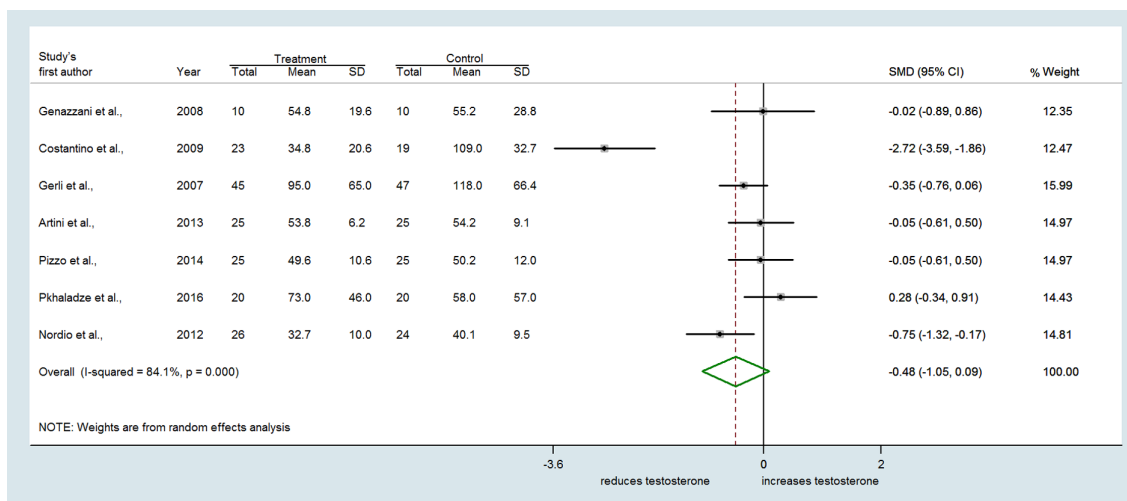


Figure 4
Forest plots showing effect sizes (SMD) for testosterone in women with PCOS.

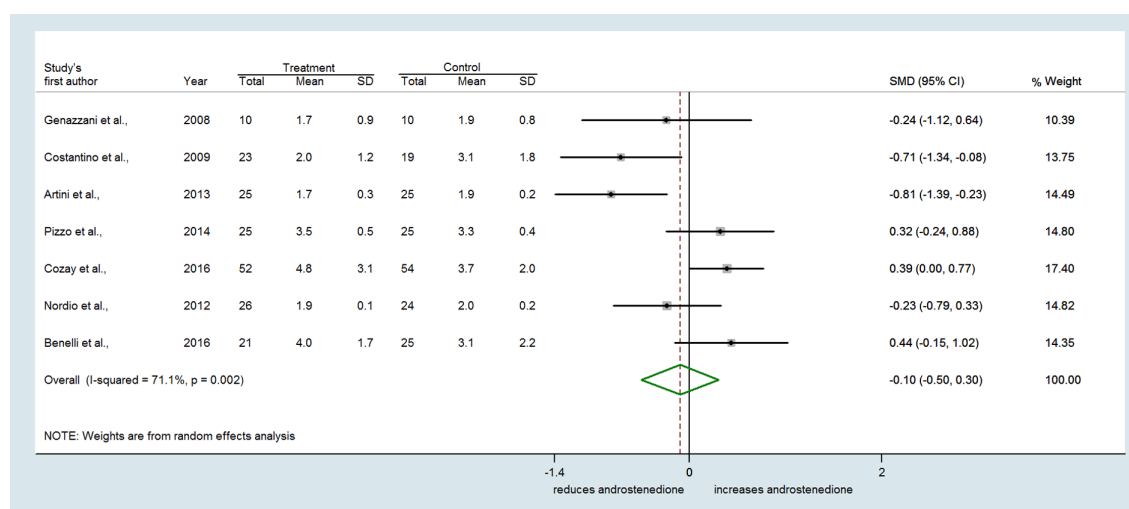


Figure 5
Forest plots showing effect sizes (SMD) for androstenedione in women with PCOS.

Discussion

The current meta-analysis highlights the beneficial effect of inositol(s) supplementation, namely MI in improving the metabolic profile of PCOS patients. Indeed, grouping the nine eligible studies, results revealed differences in the treatment effect on fasting serum insulin and on the HOMA index, both of them being significantly decreased after MI supplementation. In this study, through the use of TSA, it was illustrated that the findings on the primary outcome are conclusive. Less clear changes could be demonstrated on androgenic hormones. Circulating androstenedione levels were

unaffected by MI, while a trend toward a decrease of total testosterone occurred. Moreover, a significant increase of serum SHBG compared to other treatments was reported only in those trials which supplemented inositol(s) for at least 24 weeks.

These findings were limited by differences in the inclusion criteria of the studies, non-uniform definitions of PCOS and diversity in the components of the intervention such as dose and duration. All these factors therefore explain the high heterogeneity statistically demonstrated along with the effects.

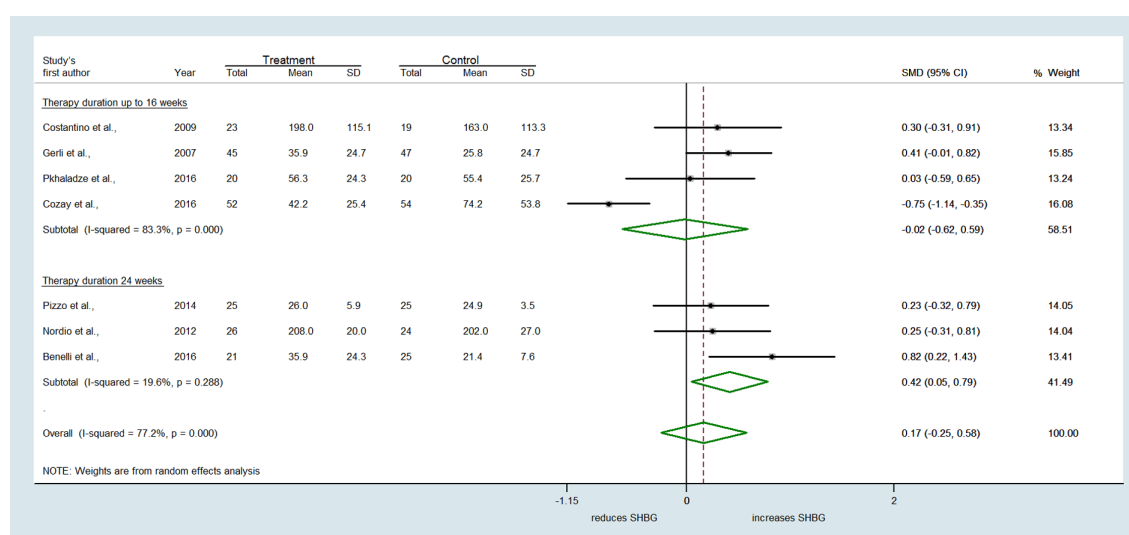


Figure 6
Subgroup meta-analysis for SHBG stratifying the studies by treatment duration (MI up to 16 weeks or 24 weeks).

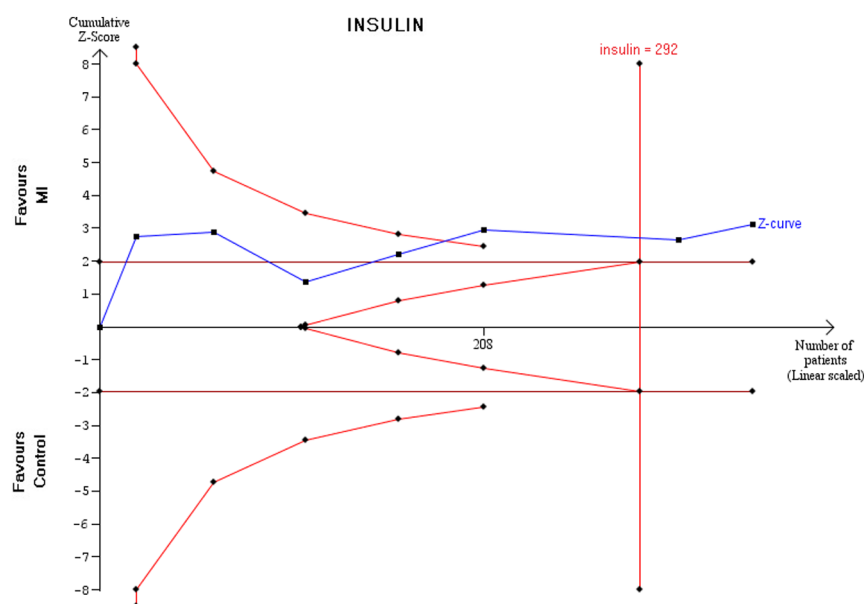


Figure 7
Trial sequential analysis on insulin outcome.

MI is the most abundant form of inositol in humans. It can turn into various derivatives through either epimerization, phosphorylation or methylation of its hydroxyl groups. The NAD/NADH epimerase, an insulin-dependent enzyme, converts MI into DCI, depending on the specific needs of the tissue for these two molecules (57, 58). Indeed, different tissues have a typical conversion rate and consequently show different MI/DCI ratios (for instance, in the ovary, it is 100:1) (59). The epimerase activity is reduced in the tissues of type 2 diabetic rats (60). There is evidence that MI to DCI conversion rate is impaired in PCOS patients due to IR; this aberration is exacerbated when having first-degree diabetic relatives (41, 58). The pathology itself or the familial predisposition negatively affects the epimerase activity, thus increasing IR and compensatory hyperinsulinaemia (61). Indeed, lower levels of DCI reduce the availability of IPGs triggering the onset of IR (62, 63). Baillargeon and coworkers have demonstrated an increase of DCI urinary excretion in PCOS women compared to normal controls accompanied by a decrease of plasma DCI concentrations (11, 64). However, no difference was found in MI concentration (64). It has been shown how administration of small DCI doses can restore insulin sensitivity and improve the hormonal pattern in obese hyperinsulinemic PCOS patients and even more if having diabetic relatives (41, 61). This specific effect might be due to its recognized insulin-sensitizing action at the systemic level. Therefore, the administration of DCI along with MI might have a greater beneficial effect when the epimerase conversion is impaired in insulin-resistant tissues to compensate

for the low endogenous DCI synthesis and its excessive urinary excretion, as well as ensuring the required tissue content of DCI derivatives. Ovaries, differently from other tissues, never become insulin-resistant (65, 66, 67). From this observation, it has been speculated that PCOS patients with hyperinsulinemia may have an accelerated MI to DCI epimerization, resulting in an overproduction of DCI and consequently an MI deficiency in the ovary (68, 69). The well-known 'DCI paradox' hypothesizes that only MI has a beneficial effect on the ovary (70). This theory has been later confirmed by a recent study showing that the oocyte quality and ovarian response have been progressively worsened by the increased dosage of DCI (71). Therefore, DCI supplementation alone is not recommendable for several reasons: (a) high doses of DCI/day have been considered toxic to ovaries and oocyte maturation (71); (b) DCI is not converted into MI; therefore, the specific action exerted by the last one would be lost; (c) MI and MI-IPG deficiencies are correlated with many IR conditions. Since MI competes with glucose for cellular transporters, a low MI intracellular uptake and increased urinary loss of MI may lead to high blood glucose levels. It can be supposed that adequate MI intake and body storages might derive the epimerase by substrate mass action inducing DCI synthesis. This agrees with the clinical evidence that reported the beneficial effect exerted by MI and DCI combined at 40:1 ratio in PCOS patients (51, 52). Further investigations might be required as also suggested by other researchers (72).

Hyperinsulinemic IR has been shown to play a pivotal pathogenic role in the endocrine and metabolic

abnormalities of PCOS (73, 74). The improvement of insulin sensitivity and the reduction of serum insulin demonstrated by MI supply are of paramount importance for ameliorating the clinical features of women with PCOS (75). The CIs for the selected studies were relatively narrow and displayed effect sizes that may be clinically relevant. These findings, therefore, support the practice of treating PCOS women with MI, either alone or in combination with DCI, to improve their endocrine and metabolic profiles.

Treatment duration seems crucial, as far as androgen profile is concerned. This agrees with the previous observation on acne, whose improvement with MI required at least 6 months supplementation (45).

Indeed, insulin affects the androgenic state not only directly by interfering with metabolism of ovarian androgens, but also indirectly by decreasing circulating SHBG levels (32). SHBG is a protein that binds to testosterone, making it unavailable to target tissues. Higher levels of SHBG lead to lower bioavailability of testosterone, thus minimizing the hyperandrogenic features. Furthermore, SHBG appears to be a potentially valuable marker of IR in PCOS (76). Interventions improving insulin sensitivity and reducing circulating insulin, such as metformin, troglitazone and pioglitazone, have been shown to reduce circulating testosterone and increase serum SHBG levels (77, 78, 79). Clinical studies suggested that metformin, used as an antidiabetic drug, may improve insulin sensitivity in obese women with PCOS by restoring an inositol-based signaling (61, 80). Nonetheless, these drugs have been reported to be associated with adverse effects (81). Indeed, metformin, the most common insulin-sensitizing agent for PCOS (82, 83, 84, 85, 86), significantly induces nausea, abdominal distress and diarrhea, thereby reducing patients' compliance (87, 88). MI is generally well tolerated across the range of therapeutic dosages (89), with the exception of minor side effects reported at higher concentration. Interestingly, in this meta-analysis, the tolerability profile of MI is considered to be quite agreeable. Among the studies, only Gerli and coworkers reported side effects on the dosage regimen commonly used (49).

The growing interest toward the clinical effects of inositols is witnessed by the recent meta-analysis which demonstrated how this supplement is effective in promoting ovulation in patients with PCOS (90). In conclusion, the present meta-analysis of nine RCTs revealed that MI alone or combined with DCI improves the metabolic profile of women with PCOS, also increasing SHBG when supplementation lasted at least 24 weeks.

Declaration of interest

Unfer V and Orrù B are employees at Lo.Li. Pharma, Rome, Italy. Giordani B has received compensation as a consultant for the meta-analysis from Lo.Li. Pharma. The other authors have no conflicts of interest.

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